Exploring new strategies in diagnosis and treatment of hilar cholangiocarcinoma

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Chapter 2

Diagnostics and Treatment of Cholangiocarcinoma

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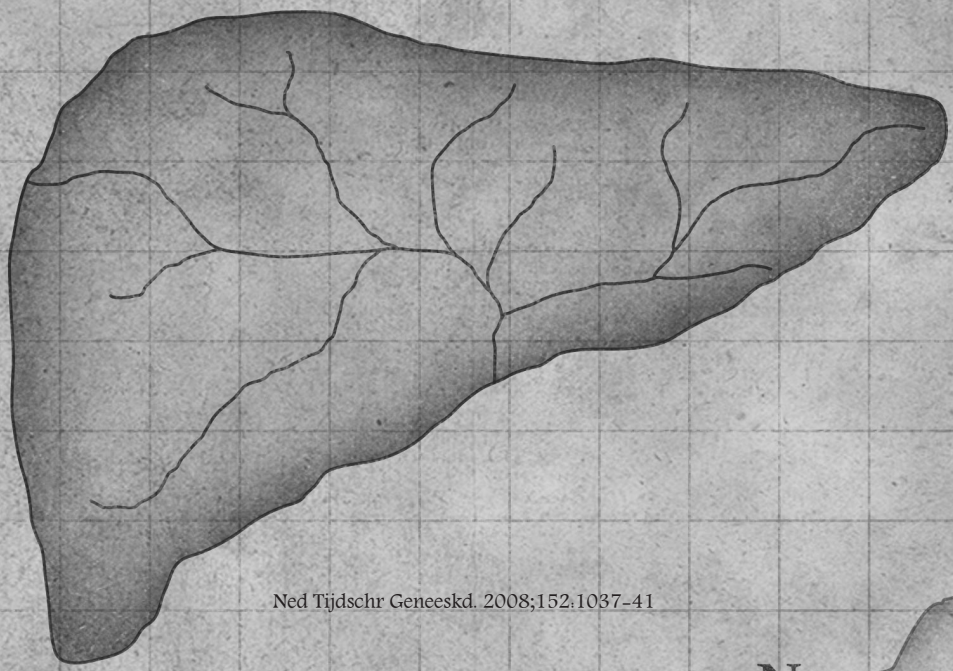

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ABSTRACT

- Cholangiocarcinoma is a rare malignancy originating from the biliary epithelium. The disease can arise anywhere in the biliary tract: intrahepatic, perihilar or distal. The overall prognosis for cholangiocarcinoma is poor.
- The treatment necessitates a multidisciplinary approach.
- Radical resection of the extrahepatic bile ducts, usually in combination with concomitant partial liver resection, remains the only curative treatment for hilar cholangiocarcinoma.
- Liver transplantation in combination with neoadjuvant chemoradiation therapy for unresectable hilar cholangiocarcinoma seems to be promising in a highly selected group of patients.
- Palliative treatment should be targeted at adequate biliary drainage, preferably by stenting.
- Radiotherapy and systemic chemotherapy are not standard treatment and should be applied in an experimental setting only.
- New options such as photodynamic therapy and tyrosine kinase inhibitors are promising, but still experimental treatments.

INTRODUCTION

Cholangiocarcinoma is a malignant disease originating from the biliary epithelium. The exact incidence of the disease is unknown, but estimations in the United States are 1-2 cases per 100.000 persons per year, ranking cholangiocarcinoma as the second commonest primary liver tumor worldwide.[1] In Western countries, the most important risk factor for developing cholangiocarcinoma is primary sclerosing cholangitis (PSC), which is a progressive biliary disease characterized by inflammation, fibrosis and stenosis of the intrahepatic and extrahepatic bile ducts.[2] The prevalence of cholangiocarcinoma in patients with PSC is 7-13% and thereby increased compared to the general population.[2] The annual risk to develop cholangiocarcinoma in the presence of PSC is 0.5 – 1.5%.[3] Other risk factors are parasitic liver infections (liver fluke), hepatolithiasis, Caroli's disease and congenital choledochal cysts. Chronic inflammation and the consequential biliary duct cell injury coupled with the obstruction of bile flow seems to be important in the pathogenesis of the tumor.[4] Most tumorsm however, arise in the absence of distinct risk factors.

Radical surgical resection of the tumor is the only chance for curation. Improved surgical techniques have made more patients eligible for surgery. Although cholangiocarcinoma is known as a rapidly progressive disease with a median survival of a few months without treatment, patients are able to survive one to two years provided that biliary drainage is secured.

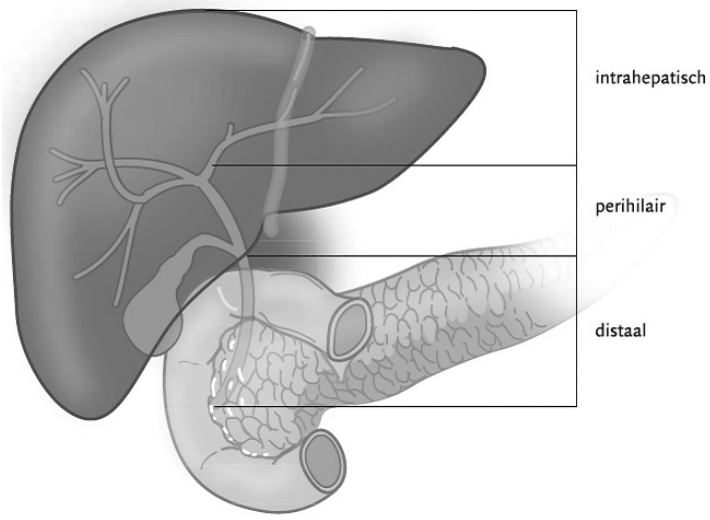

Figure 1 ***(adopted from the original article).*** **Cholangiocarcinoma is divided into three subtypes based on its anatomic location. (see color image on page 147)**

This article presents an overview of the current insights and recent developments in staging and treatment of cholangiocarcinoma.

DIAGNOSIS

Cholangiocarcinoma can arise anywhere along the biliary tract. There are three distinct categories based on the anatomic location of the tumor: intrahepatic, perihilar and distal (figure 1).[5]

More than 90% of cholangiocarcinomas are adenocarcinomas. These can be further divided into three types based on morphological features: mass forming tumors, periductal infiltrating tumors and intraductal growing tumors.[6] Intrahepatic tumors make up for 10% of all cholangiocarcinomas and usually consist of the mass forming type.[6,7] Perihilar tumors, also known as Klatskin tumors, arise at the confluence of the left and right hepatic duct and are the most frequent subgroup, accounting for 60-70% of cases, and usually consist of the periductal infiltrating type. These tumors have a branchlike appearance, spreading longitudinally along the axis of the bile duct wall, partially in the submucosal space with perineural, perilymphatic and perivascular infiltration.[6] The specific growth pattern results in an irregular stenosis of the bile duct with ultimately complete bile flow obstruction. A new staging system has been proposed, in which in addition to the localization and extension of the tumor, also the presence or absence of portal venous invasion and the presence or absence of liver lobe atrophy is taken into account.[8] This staging system seems to correlate with the resectability rate and survival. Distal cholangiocarcinomas are the third subgroup of tumors (20-30%) and are located between the orifice of the cystic duct and the ampulla of Vater (figure 1)[9]

Patients with intrahepatic tumors sometimes present with abdominal pain located in the right-upper quadrant. Patients with hilar tumors often present with jaundice secondary to biliary obstruction or fever because of cholangitis. Patients with distal tumors usually present with jaundice too. In contrast to hilar cholangiocarcinoma, distal tumors can cause gallbladder enlargement. Courvoisier's sign (jaundice and a non-tender enlarged gallbladder) is specific for distal biliary obstruction.

Liver function tests usually show cholestasis without elevated liver enzymes. There is no specific marker for cholangiocarcinoma, but carbohydrate antigen 19-9 (CA 19-9) is most frequently used. In patients with PSC an elevated CA 19-9 of >100 U/mL has a sensitivity of 89% and a specificity of 86% for cholangiocarcinoma. In patients without PSC the sensitivity

is 53%.[7]

Ultrasound investigation is able to detect dilated bile ducts proximal to the obstruction, but the tumor itself can rarely be identified.[10] Computer tomography (CT) is used to identify intrahepatic tumors, dilated bile ducts and enlarged lymph nodes. This technique also allows excellent assessment of the vascular anatomy. However, the extent of intraductal invasion is usually underestimated and hilar tumors are often difficult to visualize on CT.[10]

Currently, magnetic resonance cholangiopancreatography (MRCP) is the optimal imaging modality for the detection of cholangiocarcinoma.[2,11] Magnetic resonance imaging produces reliable information regarding liver and biliary anatomy and extension of the tumor. MR angiography is used to evaluate the relationship between the tumor and nearby vascular structures.[12] Image quality of MRCP is comparable to endoscopic retrograde cholangiopancreatography (ERCP). During ERCP it can be difficult to assess the amount of tumor extension towards the liver. In contract to MRCP, ERCP is an invasive procedure accompanied by a risk of perforation, bleeding and post procedural pancreatitis and cholangitis. However, ERCP has the advantage of obtaining cytology from the bile ducts. Unfortunately, cytology is often negative, especially in the case of hilar tumors, because of their specific periductal infiltrative growth pattern together with an extensive desmoplastic (fibrotic) reaction.[13]

Percutaneous transhepatic cholangiography (PTC) as imaging technique is absolutely contra-indicated because of the possible induction of implantation metastases along the catheter tract.[14] Cholangioscopy, which is possible through the working channel of a duodenoscope during ERCP, allows direct visualization of the bile ducts and subsequent carefully aimed biopsies.[15] Although positron emission tomography (PET) is currently not part of the standard work-up for cholangiocarcinoma, the technique can be useful for the detection of distant metastases.[11]

CURATIVE INTENT TREATMENT

Surgical resection. The treatment of intrahepatic cholangiocarcinoma consists of surgical resection of the affected liver segments. Five-year survival rates after surgical treatment of intrahepatic cholangiocarcinoma are 27-48%.[11] Distal cholangiocarcinoma, like other tumors around the ampulla of Vater, is treated by conventional pancreatoduodenectomy (Whipple procedure) or pylorus preserving pancreatoduodenectomy.[2,16] Five-year survival after

resection of distal cholangiocarcinoma is around 40%.[17]

For the treatment of hilar cholangiocarcinoma it has become clear that radical resection of the extrahepatic bile ducts in combination with partial liver resection including the caudate lobe offers the best chance for curation.[18] Obtaining tumor free resection margins (a so called R0 resection) can be difficult because of the close proximity of the hepatic artery and portal vein to the tumor. Resection of the extrahepatic bile ducts without concomitant partial liver resection is obsolete because of the high percentage of positive resection margins.[8]

Recent studies in which extrahepatic bile duct resection was combined with partial liver resection and sometimes portal vein resection and reconstruction report five-year survival rates of 30-40%. [8,19-22] One study showed a five-year survival rate of 72% in patients undergoing right extended hemihepatectomy together with portal vein resection and reconstruction.[9] When the future liver remnant is too small (less than 25% of the original liver volume) a step-up procedure can be followed. Percutaneous embolization of the right portal vein is carried out, resulting in contralateral hypertrophy of the future liver remnant. When hypertrophy is confirmed, extended right hemihepatectomy can be performed under safer conditions.[23]

Contraindications for resection of cholangiocarcinoma are bilateral involvement of the hepatic artery or portal vein or bilateral extension beyond the secondary biliary branches.[11] According to recent insights preoperative biliary drainage is not mandatory in the case of distal biliary obstruction, however in patients with biliary obstruction at the level of liver hilum who are eligible for partial liver resection preoperative biliary drainage should be attempted.[24]

In most studies the presence of regional lymph node metastases is an important prognostic factor for survival next to tumor stage, tumor grade and radical resection.[19,21,25] Five-year survival after curative intent resection without lymph node metastases is around 45% and drops rapidly to 0-28% in case lymph node metastases are present in the resected specimen.[20,21] Figure 2 shows the survival of 49 patients who underwent combined extrahepatic bile duct resection with partial liver resection for hilar cholangiocarcinoma between 1986 and 2006 at the University Medical Center Groningen according to lymph node status.

It is very difficult to identify lymph node metastases prior to surgery using the current imaging modalities.[10] Diagnostic laparoscopy is used for assessing liver and peritoneal metastases, but it is not possible to detect vascular invasion and lymph node metastases with this technique.[26] Lymph node metastases are usually found at the time of surgery or at pathological investigation of the resected specimen. The value of preoperative endoscopic

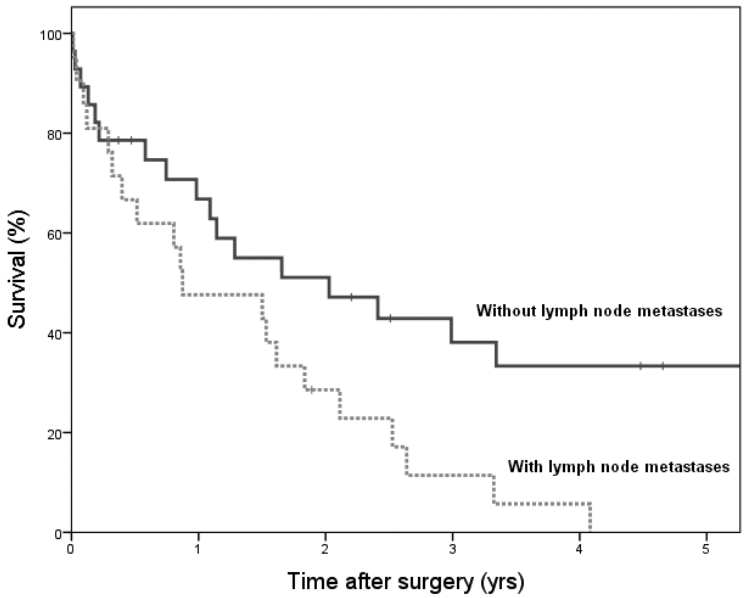

Figure 2. Survival analysis of 49 patients with hilar cholangiocarcinoma who underwent extrahepatic bile duct resection in combination with partial liver resection at the University Medical Center Groningen between September 1986 and October 2006. Survival of patients without lymph node metastases (straight line, n=28) was significant better compared to patients with lymph node metastases (dotted line, n=21). (Logrank test P=0.02). (see color image on page 147)

ultrasound with fine needle aspiration of regional lymph nodes for cytology is currently being investigated.[27]

Liver Transplantation. Patients with hilar cholangiocarcinoma often present in advanced stages of disease or suffer from an underlying parenchymal liver disease such as fibrosis or cirrhosis, for example in the setting of PSC, excluding partial liver resection as a treatment option. [28] This group could benefit from liver transplantation because total hepatectomy followed by orthotopic liver transplantation provides wide resection margins, without the risk of decompensation of the cirrhotic liver. Unfortunately, the early experience of liver transplantation for hilar cholangiocarcinoma has been disappointing due to low survival rates.[28]

Recenly, however, promising results have been published regarding the use of a strict neo-adjuvant protocol followed by liver transplantation for patients with unresectable hilar cholangiocarcinoma. Five-year survival in this group was 74%.[29] The neo-adjuvant protocol consisted of a combination of external beam radiotherapy and intraluminal brachytherapy

with chemosensitization. Strict selection of the group was important which was highlighted by the fact that the protocol could be completed in approximately 60% of patients.[30]

PALLIATIVE TREATMENT

Many patients with cholangiocarcinoma are not eligible for curative treatment anymore and receive palliative treatment. The aim of palliative treatment is to improve quality of life and alleviate symptoms as jaundice, cholangitis and pain. The basis of palliative care is to secure biliary drainage by surgical, endoscopic or percutaneous interventions. In most cases non-operative drainage of the bile duct is preferred (stenting). Survival after palliative surgery is comparable to endoscopic stent placement, but the latter is associated with less short-term mortality and morbidity.[31] There are plastic and self-expandable metal stents. Plastic stents are easier to insert and less expensive, but metal stents have a longer patency and therefore decreased risk for cholangitis. Metal stents are used in patients with a longer life expectancy.[2] If endoscopic stent placement is impossible, ultrasound guided percutaneous drainage of bile flow can be performed.[32]

Chemotherapy. The value of chemotherapy in the treatment of unresectable cholangiocarcinoma is not yet determined. So far, adequately designed randomized trials of sufficient size showing an improvement in quality of life or survival with the use of chemotherapy have not been performed. Of all chemotherapeutical regimes, it seems that a combination of platinum-based agents with gemcitabin or a fluorouracil analog are most promising for future research.[33] As long as the efficacy of chemotherapy for unresectable cholangiocarcinoma remains to be determined, it should be used in clinical trials only.

Radiotherapy. There is no prospective, controlled evidence that external beam radiotherapy has a beneficial effect on the survival or quality of life for patients with unresectable cholangiocarcinoma. However, radiotherapy may be useful in patients with specifically localized pain, insufficient biliary drainage despite stents or uncontrollable bleeding.[2] Again, treatment should preferably be used in the setting of clinical research.

New developments. In recent years, a number of novel experimental techniques have been introduced with sometimes promising results. One potential treatment is photodynamic

therapy, which consists of an intravenously administered photosensitizer followed by endoscopic insertion of a probe in the bile ducts that emits light at a specific wavelength. This induces tumor cell necrosis. Prospective, randomized studies describing the technique report improved biliary drainage, quality of life and gain in survival of a few months.[34,35] On the other hand, photodynamic therapy can be demanding for the patient, it sometimes induces increased light sensitivity of the skin and there is an increased risk of cholangitis.

Another technique aiming for local tumor control is the use of endoluminal brachytherapy sometimes combined with external radiotherapy.[36] Recent experimental studies regarding the systemic use of tyrosine kinase inhibitors show promising results.[37] Other new techniques are the use of experimental Y-shaped bile duct stents[38] and transarterial chemo-embolization.[39]

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